

5 or Q41R; (3) a Group 4 amino acid residue mutated to a Group 2 amino acid residue at position 52, for example, the mutation represented by T52I; (4) a Group 4 amino acid residue mutated to a Group 3 amino acid residue at position 52, for example, the mutation represented by
10 T52N; (5) a Group 4 amino acid residue mutated to a Group 5 amino acid residue at position 73, for example, the mutation represented by C73R; (6) a Group 1 amino acid residue mutated to a Group 4 amino acid residue at position 101, for example, the mutation represented by
15 P101S; (7) a Group 1 amino acid residue mutated to a Group 3 amino acid residue at position 101, for example, the mutation represented by P101Q; (8) a valine amino acid residue mutated to another Group 2 amino acid residue at position 111, for example, the mutation represented by
20 V111I; (9) a Group 4 amino acid residue mutated to a Group 2 amino acid residue at position 133, for example, the mutation represented by S133L; (10) a Group 3 amino acid residue mutated to a Group 2 amino acid residue at position 141, for example, the mutation represented by
25 E141V; (11) a Group 3 amino acid residue mutated to a Group 5 amino acid residue at position 141, for example, the mutation represented by E141K; (12) a Group 4 amino acid residue mutated to Group 6 amino acid residue at position 153, for example, the mutation represented by
30 C153Y; (13) a Group 4 amino acid residue mutated to a Group 5 amino acid residue at position 153, for example, the mutation represented by C153R; (14) a Group 4 amino acid residue mutated to a Group 1 amino acid residue at position 281, for example, the mutation represented by
35 T281A; (15) a Group 3 amino acid residue mutated to a Group 2 amino acid residue at position 367, for example, the mutation represented by N367I; (16) a Group 3 amino acid residue mutated to a Group 6 amino acid residue at position 367, for example, the mutation represented by
40 N367Y; (17) a Group 1 amino acid residue mutated to Group 4 amino acid residue at position 389, for example, the mutation represented by P389S; and/or (18) a Group 1 amino acid residue mutated to a Group 2 amino acid residue at

5 position 389, for example, the mutation represented by P389L.

In certain embodiments of this aspect of the invention, the variant protein of the lovE protein sequence has an amino acid sequence of SEQ ID NO:41, SEQ
10 ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID
15 NO:62, SEQ ID NO:63, SEQ ID NO:64, or SEQ ID NO:65.

In another embodiment thereof, the variant protein of the lovE protein is encoded by a nucleic acid molecule having a polynucleotide sequence of SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID
20 NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, or SEQ ID NO:90.

25 In a sixth aspect, the invention provides a fungus having improved lovastatin production made by the process of transforming a fungal cell with a nucleic acid molecule encoding a variant of the lovE protein of the first aspect of the invention. In an embodiment thereof, the nucleic
30 acid molecule is selected from a nucleic acid molecule of the second aspect of the invention.

In a seventh aspect, the invention provides an improved process for making lovastatin comprising transforming a fungal cell with a nucleic acid molecule
35 encoding a variant of the lovE protein of the first aspect of the invention. In an embodiment thereof, the fungal cell is transformed with a nucleic acid molecule of the second aspect of the invention.

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40 discloses lovastatin production genes. However, this reference does not provide a mature *lovE* cDNA sequence. The invention herein remedies the shortcoming of this

5 reference by providing a complete cDNA sequence for the *lovE* mRNA.

In an eighth aspect, the invention provides a nucleic acid molecule encoding a *lovE* protein defined by SEQ ID NO:91. In an embodiment thereof, the invention provides
10 an isolated *lovE* nucleic acid molecule defined by SEQ ID NO:92.

The following examples illustrate the preferred modes of making and practicing the present invention but are not meant to limit the scope of the invention since
15 alternative methods may be utilized to obtain similar results.

EXAMPLES

20 **Example 1: Preparation of Strains and Plasmids**

Strain MY2124 was derived from the Sigma 1278b strain background of *S. cerevisiae* and its complete genotype is as follows: *MAT α /MAT α ::LEU2 ura3 Δ 0 /ura3 Δ 0 leu2 Δ 0/leu2 Δ 0 trp1 Δ 0::*hisG*/trp1 Δ 0::*hisG* his3 Δ 0::*hisG*/his3 Δ 0::*hisG*
25 *ura3 Δ 0::*lovF-HIS3p-neo*/ura3 Δ 0. MY2124 can be constructed by mating *S. cerevisiae* strains MY2112 (*MAT α ura3 Δ 0 leu2 Δ 0 trp1 Δ 0::*hisG* his3 Δ 0::*hisG* ura3 Δ 0::*lovFp-HIS3p-neo*) with MY1555 (*mat α ::LEU2 ura3 Δ 0 leu2 Δ 0 trp1 Δ 0::*hisG* his3 Δ 0::*hisG*) and isolating zygotes. The *ura3 Δ 0::*lovFp-HIS3p-neo* allele of MY2112 was derived by cotransforming *Sfi*I-linearized plasmid MB2254 with pRS424 (Sikorski and Hieter (1989) *Genetics* 122:19-27) into MY1413 (*MAT α leu2 Δ 0 trp1 Δ 0::*hisG* his3 Δ 0::*hisG*). Transformants were selected on SC-Trp media and subsequently screened for 5-fluoro-orotic acid resistance to identify those
30 transformants containing the *ura3 Δ 0::*lovFp-HIS3p-neo* allele. Trp⁻ segregants lacking plasmid pRS424 were isolated by growing the strain under non-selective conditions.*******